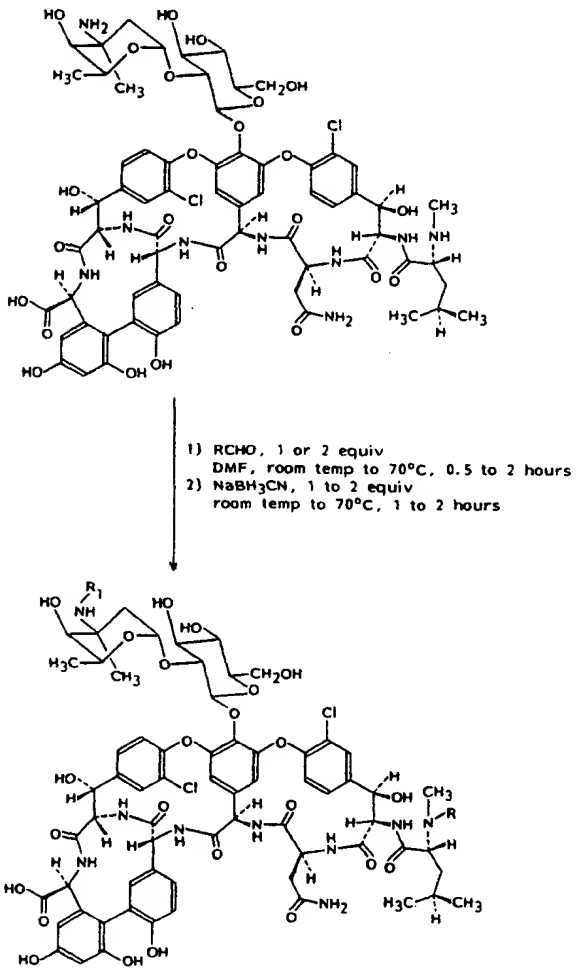
Fig. 1. Synthesis of *N*-alkyl vancomycins.



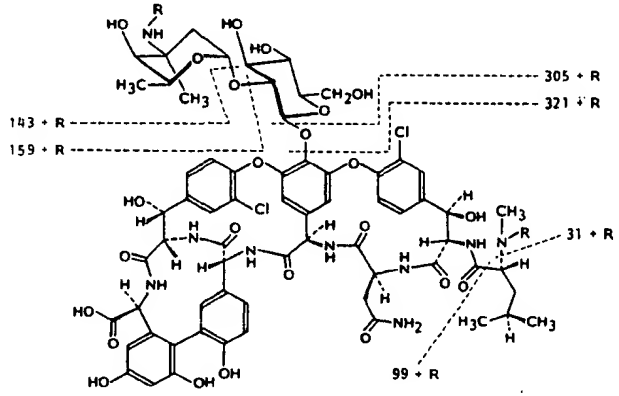
Two mono-*N*-alkyl and one di-*N*-alkyl vancomycins

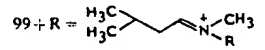
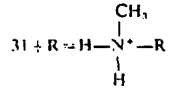
cosamine fragments, whereas the devancosamine vancomycin, aglucovancomycin, and *N*-methyl leucine fragments show increased mass corresponding to the alkyl residue. The mono-*N*-alkyl vancomycin substituted on vancosamine gives vancosaminyl-*O*-glucose and vancosamine fragments containing the additional mass due to alkylation on the amino group of vancosamine.

SAR of *N*-Alkyl Vancomycins

The first derivatives prepared were the *N*-decyl vancomycins with an aliphatic straight chain

Fig. 2. FAB-MS fragmentation pattern of *N*-alkyl vancomycins.



R on vancosamine	R on leucine
M+H=Vancomycin+R+H=1,447+R+H	M+H=Vancomycin+R+H=1,447+R+H
1,305=Devancosamine vancomycin+H	1,305+R=Devancosamine vancomycin+R+H
1,143=Aglucovancomycin+H	1,143+R=Aglucovancomycin+R+H
143+R=Vancosamine+R	
159+R=Vancosamine+R+oxygen	99+R= 
305+R=Vancosamine+glucose+R	
	31+R= 

similar to the naturally occurring *N*-acylamido glycopeptides.[1-6] A comparison of the antibacterial activities of the *N*-decyl vancomycins with the corresponding *N*-decanoyl vancomycins shows that the C_{10} alkyl analogs are more active than the corresponding alkanoyl series. Furthermore, the mono-*N*-decyl vancomycin 5 is more active *in vitro* than the parent vancomycin, equivalent to vancomycin *in vivo*, and shows longer elimination half-life in rats. Encouraged by this result, we undertook an extensive SAR of *N*-alkyl vancomycins, and over eighty derivatives were prepared and evaluated.

A series of the two mono-*N*-alkyl and one di-*N*-alkyl derivatives belonging to nine aliphatic and five aromatic *N*-alkyl vancomycins were prepared and their antibacterial activity compared. As in the SAR of the *N*-acyl vancomycin series,[8] the general trend is that the *N*-alkyl derivatives substituted on vancosamine are more active than those substituted on *N*-methylleucine, and both mono-substituted vancomycins are more active than the corresponding di-*N*-alkyl vancomycins.

Having established that the mono-*N*-alkyl vancomycins substituted on vancosamine are the most active of the three derivatives, the reaction conditions for compounds described on Table 3 were adjusted so that the most active mono-*N*-alkyl derivative was the major product of the reaction. The other product for the ten series of compounds in Table 3 were either the other mono-*N*-alkylated derivative or the di-*N*-alkyl compound.

The *in vitro* and *in vivo* antibacterial activity of all thirty-eight mono-*N*-alkyl vancomycins substituted on vancosamine were determined. The pharmacokinetics of the most active derivatives and